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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,471	02/22/2002	Helmut M. Sassenfeld	3091-A	8482

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,471	SASSENFELD ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *8,12,13,34,38 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9-11, 14-33, 35-37 and 40-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-55* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10/16/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-55 are pending in the instant application.

Election/Restrictions

2. Applicant's election of protein species of a soluble form of TNF receptor and reduction/oxidation coupling agent that is cysteine in the Paper filed Oct. 16, 2003 is acknowledged.

Claims 1-7, 9-11, 14-33, 35-37 and 40-55 are currently under examination.

Claims 8, 12, 13, 34, 38 and 39 have been withdrawn as being drawn to non-elected species.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 9-11, 14-27, 30-33, 35-37 and 40-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merli et al., Analytical Biochemistry, Sept 1., 1995, Vol. 320, No. 1, pages 85-91, and further in view of Beutler et al., U.S. Patent No. 5,447,851, Sept. 5, 1995, Grossenbacher et al., U.S. Patent No. 5,661,001, August 26, 1997, Purchio et al., EP 0 293 785, Dec. 7, 1988, and Thomas, U.S. Patent No. 5,879,673, March 1999.

Claims 1-7, 9-11, 14-27, 30-33, 35-37 and 40-55 encompass a method contacting a preparation of a recombinant form of a soluble TNF receptor (which may be an Fc fusion protein) produced by mammalian cells with a reduction/oxidation coupling agent which is cysteine, and isolating a fraction of the preparation of the recombinant protein with a desired conformation wherein the desired conformation has a higher binding affinity for TNF-alpha, at the various pH's listed in the claims, wherein the preparation of recombinant protein has been purified from a Protein A or Protein G column, and wherein the contacting step is performed at about 25°C or 4°C, and wherein the contacting step is quenched by acidification, and wherein the isolating step comprises one or more chromatography steps, and wherein the protein concentration is from about 0.5 to about 10 mg/ml, and wherein the ratio of reducing thiols in the reduction/oxidation coupling reagent to disulfide bonds in the protein is about 320:1 to about 64,000:1, wherein the TNF receptor is formulated into or sterile bulk form or sterile unit dose form, and pharmaceutical composition produced by the method.

Merli et al. teach optimization of refolding of soluble tumor necrosis factor receptor type I produced in *E. coli* cells, determined by renaturation under various conditions including

different times (0.5 to 7 days), protein concentrations (7-35 ug/ml), pH (6.5 to 9) and temperatures (4, 25 and 37°C), and purification of renatured protein by chromatography. Merli also teaches that optimal pH of refolding is 8.5 when in the presences of arginine (pages 88-89), and production of soluble TNF receptor in CHO cells (glycosylated). Merli et al. also teaches that methodologies for recombinant protein denaturation are well established and almost standardized, while refolding conditions usually must be determined empirically for each protein (page 90, second column). Merli et al. does not teach that the soluble tumor necrosis factor receptor is fused to Fc, or cysteine as reduction/oxidation coupling reagent.

Beutler et al. teach the extracellular domain of 55 kD TNF receptor fused to Fc (claim 1 for example), recombinant production of the protein in mammalian cells (claim 42, for example), and that such a chimeric protein is more stable when administered in vivo than an unfused protein (column 3, line 61 to column 4, line 14), purification from a Protein A column (column 4, lines 49-68), and separation of proteins using chromotagrophy (column 18, lines 55-60), and use of the recombinant TNF receptor to treat various disorders (column 23, line 1 to column 26, line 9).

Thomas teaches that oxidized and reduced glutathione or oxidized and reduced cysteine can be the redox reagent pair during renaturation of proteins.

Grossenbacher et al. teach that proteins produced in bacterial hosts or which are otherwise in a denatured or non-native form can be renatured using reducing conditions to facilitate correct folding and denaturant replacement in presence of air or other oxidizing agents to reform the disulfide bonds, and cite numerous references as being merely representative of a huge amount of literature dealing with the refolding of non-native proteins derived from

different sources. Grossenbacher et al. also teach that the man skilled in the art on the other hand knows that the success of refolding experiments cannot be predicted (column 4, line 44 to column 5, line 15), and also the refolded protein may be purified by chromotagraphy (column 13, lines 8-12).

Purchio et al. teach that high level expression of eukaryotic proteins in CHO cells may lead to unnatural crosslinking of disulfide bonds which results in inactive proteins (page 12, lines 46-48), and that acidification can be used to quench a reduction reaction (page 35, second paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize renaturation conditions for a soluble TNF receptor, as taught by Merli et al., in order to produce correctly folded, and therefore active, protein that would efficiently bind TNF-alpha. Although Merli et al. teach renaturation of protein produced by prokaryotic cells, which often express eukaryotic proteins in a denatured inactive form, Purchio et al. teach that recombinant proteins produced in eukaryotic cells may also be inactive due to unnatural crosslinking of disulfide bonds, so one of ordinary skill in the art would be motivated to optimize protein produced in eukaryotic cells as well. Grossenbacher et al. is further evidence that it was standard in the art of recombinant protein production at the time the invention was made to experimentally determine correct refolding of non-native proteins from different sources in order to reform disulfide bonds by oxidizing agents and to purify such proteins using chromatography, while Thomas teaches that oxidized and reduced cysteine can be the redox reagent pair during renaturation of proteins. One of ordinary skill in the art would be motivated to optimize such renaturation conditions for a soluble TNF receptor Fc fusion protein produced

by mammalian cells, as taught by Beutler et al., since soluble TNF receptor can be used pharmaceutically to treat various disorders, and since the Fc fusion is more stable when administered in vivo than an unfused TNF receptor and would therefore be more effective as a therapeutic agent, and also since production in a mammalian cell would produce a glycoslyated form of the protein, which is the naturally occurring form of the protein. It would also have been *prima facie* obvious to prepare pharmaceutical compositions comprising such renatured soluble TNF receptor Fc fusion proteins, since the art teaches the importance of such proteins therapeutically. There would have been a reasonable expectation of success, since soluble TNF receptor Fc fusion protein had been made in the prior art, and since methods of optimizing refolding of soluble TNF receptor had been accomplished in the prior art, and also since methods of refolding denatured proteins were well known and successfully utilized by those of ordinary skill in the art.

Conclusion

4. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (571) 272-0871.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner